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Biological monitoring of workers exposed to engineered nanomaterials

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Abstract

As the number of nanomaterial workers increase there is need to consider whether biomonitoring of exposure should be used as a routine risk management tool. Currently, no biomonitoring of nanomaterials is mandated by authoritative or regulatory agencies. However, there is a growing knowledge base to support such biomonitoring, but further research is needed as are investigations of priorities for biomonitoring. That research should be focused on validation of biomarkers of exposure and effect. Some biomarkers of effect are generally non-specific. These biomarkers need further interpretation before they should be used. Overall biomonitoring of nanomaterial workers may be important to supplement risk assessment and risk management efforts.

Keywords

Hazard identification; Exposure assessment; Risk management

1. Introduction

The utility and novelty of engineered matter at the nanoscale is driving a revolution in science and commerce (Roco, 1997; Stirling, 2018). Engineered nanomaterials (ENMs) offer the opportunity to make products lighter, stronger, more conductive, and generally “smarter” (Iavicoli et al., 2014a,b; Navya and Daima, 2016; Thiruvengadam et al., 2018). ENMs entered commerce in the early 2000s and found utility in many sectors and commercial products. Indeed, workers have been and are expected to be increasingly involved and exposed to ENMs in various applications as well as along their whole life-cycle, from research to end-life or recycling (Schulte et al., 2016).

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Simultaneously, occupational health concerns have emerged regarding the possible impact of such nano-sized materials on the health of exposed employees. These concerns were based on previous evidence about the effects of ultrafine particulate matter derived from air pollution epidemiological studies, data extrapolated from investigations on the health consequences of diesel and welding fume exposures that may contain incidental nanoparticles (NPs), and preliminary toxicological findings obtained in vitro and in vivo models with ENMs (Iavicoli et al., 2011, 2012, 2016; Leso et al., 2017; Oberdörster and Yu, 1999; Peters et al., 2011; Stone et al., 2017).

Assessing the occupational risks derived from ENM exposure is a challenging task. This is because of difficulties in characterizing their potential hazard due to their huge physico-chemical variability, as well as in adequately assessing environmental exposure and individual response. In fact, to date, although there has been extensive research, no standardized environmental monitoring strategies to assess workplace and breathing zone exposures, nor the physico-chemical ENM features to be measured as the most effective dose metric parameters are widely agreed upon (Brouwer et al., 2009; Brouwer, 2010; Pietroiusti et al., 2018). Similarly there are no instances of regular monitoring of nano-material workers for biomarkers of effect. This is in part likely because these markers are not specific and have not been fully validated as indicators of adverse effects of specific exposure.

Nonetheless, biological monitoring may contribute to the identification of potential hazards of ENMs and to the assessment of occupational exposure to such xenobiotics; therefore, supporting a more adequate assessment and management of risks (Schulte and Hauser, 2012). In this study, the current status of biological monitoring for ENM workers will be addressed.

2. Methods

In order to review the available scientific literature on biological monitoring, a framework matrix was employed (Fig. 1). pubMed, Scopus, and Web of Science databases were searched. Our search strategy was aimed to identify issues concerning the development and use of biomarkers that may be helpful to address the different steps along (Fig. 1) the continuum of occupational safety and health actions from hazard identification to risk management (*x*-axis) (Schulte and Hauser, 2012). Additionally, the literature related to various classes of biomarkers (*y*-axis) was assessed for each category and subcategory in the continuum. The objective of the search was to identify papers that raised issues in the use of biomarkers for a cell or cells in the matrix. These issues will be discussed under the categories of biomonitoring, epidemiological research, and medical surveillance. However, as the major findings were from toxicological research on ENMs, these will be presented to establish a foundation for thinking about the utility of various types of biomarkers for other purposes in the continuum. There is a rich literature on the validation of biomarkers that can be consulted regarding their utility (Bonassi and Au, 2002; Schulte and Hauser, 2012; Schulte and Talaska, 1995).

3. Hazard identification

Since the late 1990s, there has been a growing knowledge-base about the potential adverse effects of ENMs. This seems a challenging issue due to the diverse universe of materials characterized by combinations of a large number of physico-chemical characteristics and other parameters that may include size, shape, chemical composition, solubility, crystalline structure, charge, surface characteristics, attached functionalized groups, agglomeration, and impurities. In humans, ENMs generally have not yet been reported to cause adverse health effects (Bergamaschi, 2012). This may be due to a number of factors: the precautions adopted by the scientific and commercial communities to control exposure levels, the guidance from authoritative agencies responsible for the development of nanotechnology, the small number of involved workers, and the limited time since first exposure, which is generally 15–20 years, considering the periods that such products were introduced in commerce (Fig. 2).

Considering that nanotechnology is an enabling technology diffused through many productive sectors, the mass of produced ENMs is generally small. In these complex industrial scenarios, ENM dose-response relationships may be underestimated by the confounding influence of other possible chemical co exposures. Nevertheless, hazard research in the last 15 years has shown that some types of ENMs appears to have the ability to result in adverse effects in animals. Table 1 shows an overview of the toxicological findings. Interestingly, toxicological evidence may be helpful in extrapolating information for biological monitoring.

3.1. In vitro studies

In vitro studies provide information concerning molecular effects of ENMs on cellular models, therefore suggesting possible modes of action in relation also to the intrinsic ENM physico-chemical features. This information may be important to define the hazardous properties of such nanoscale materials, a critical step in the identification of suitable biomarkers. Different ENMs, including silver (Ag)- (Müller et al., 2018; Murphy et al., 2016), titanium dioxide (TiO_2)- (Kongseng et al., 2016; Patil et al., 2016; Renwick et al., 2001), zinc oxide (ZnO)- (Patil et al., 2016), silica (SiO_2)- (Breznan et al., 2017), magnesium oxide (MgO)-NPs (Mahmoud et al., 2016), and carbon based-NMs (Chatterjee et al., 2017; Chortarea et al., 2017; Kim and Yu, 2014), demonstrated cyto-toxic, inflammatory, and oxidative stress effects, as well as the reduction of specific cellular function in vitro models. The small ENM size, resulting in a high surface area to volume ratio, may enhance ENM biological reactivity and relative toxicity (Guichard et al., 2016; Kim and Ryu, 2013; Soares et al., 2016; Uboldi et al., 2016).

Additionally, for adequate hazard identification, the chemical nature and surface chemistry should be also considered as possible influencing factors, since differently composed ENMs, i.e., metal oxide-NPs vs multi-walled-carbon nanotubes (MWCNTs) (Xia et al., 2013), Ag-NPs vs graphene oxide nano-sheets (Ivask et al., 2015), and differently functionalized NMs (Chatterjee et al., 2017; Magdolenova et al., 2015), resulted in diverse cytotoxic effects that could be also dependent on cellular type specificity (Chatterjee et al., 2017). The crystalline structure of the nano-compounds could also affect the toxicity of some ENMs, as in the case

of anatase and rutile TiO_2-NPs (Sayes et al., 2006). Shape-dependent effects have been reported for several ENMs, including Au- and TiO_2-NPs, and carbon based-ENMs (Allegri et al., 2016; Chithrani et al., 2006; Hamilton et al., 2009; Park et al., 2003; Porter et al., 2013; Öner et al., 2017). ENMs with a high aspect ratio morphology have raised particular concern in the field of respiratory toxicology, because they may induce toxicity similar to other fibrous substances, e.g., asbestos (Donaldson et al., 2011). Overall, these data may support a different behavior of ENMs according to their primary features as well as also in relation to those properties secondarily acquired when coming in contact with different culture media (Ritz et al., 2015).

3.2. In vivo studies

In vivo studies are essential to define the toxico-kinetic and dynamic behavior of ENMs and particularly to identify early adverse effects and possible target organ damage whose investigation, through biomarkers detected in accessible biological matrices, may be important for a suitable planning of biological monitoring programs. As previously mentioned, the biomolecular interactions that ENMs may experience when in contact with biological fluids, strictly dependent on ENM exposure route, can determine the formation of the so called “protein corona,” which may affect ENM dynamic profile, and therefore, biological monitoring findings (Monopoli et al., 2012).

3.2.1. Preclinical alterations—As reported in cellular models, and also in human and animal experiments, ENMs elicited the activation of oxidative stress responses that could be monitored through the reduction in plasma levels of anti-oxidant defense systems. This was detected in workers involved in the manufacture and/or application of ENMs in Taiwan, and also found after a six month follow up period (Liao et al., 2014; Liou et al., 2012, 2016). Additionally, the increased exhaled breath condensate (EBC) concentrations of lipid, nucleic, and protein oxidation markers were detected in workers exposed to Fe_2O_3- and Fe_3O_4-NPs (Pelclova et al., 2016a), MWCNTs (Lee et al., 2015), and TiO_2-NPs (Pelclova et al., 2017a, 2017b) compared to controls. In such epidemiological investigations, a dose-response correspondence was demonstrated according to the ENM environmental monitoring concentrations (Pelclova et al., 2016a, b) as well as the increase in risk levels established through a control binding nano-tool risk assessment approach (Liao et al., 2014).

Comparably, in animal models, reductions in plasma anti-oxidant defense systems and increased levels of Reactive Oxygen Species (ROS) and malondialdehyde (MDA) could be determined with SiO_2 (Du et al.,2013; Liu and Sun, 2013), Ag (Genter et al., 2012; Martins et al., 2017), Ag-NPs in coexposure with TiO_2-NPs (Martins et al., 2017), Fe_2O_3- NPs (Sundarraj et al., 2017), and multi-walled carbon nanotube (MWCNTs) exposures (Reddy et al., 2011).

Regarding inflammatory response, blood levels of fibrinogen and pro-inflammatory cytokines were increased in workers exposed to nano-sized carbon black and MWCNTs (Fatkhutdinova et al., 2016; Liou et al., 2012; Vlaanderen et al., 2017; Zhang et al., 2014) as well as to TiO_2-NPs compared to controls (Zhao et al., 2018). Conversely, when comparing serum proteins associated with inflammatory responses in ENM exposed and not-exposed

workers in research laboratories, significant increases in CD40, TNFR2, and CD62P serum concentrations were evident during the first shift of a working week and at the end of the week in exposed employees (Glass et al., 2017). These findings may suggest an anti-inflammatory and suppressive homeostatic cellular response in relation to an immune activation.

Enhanced levels of leukotrienes were detected in the EBCs of subjects occupationally exposed to TiO_2-NPs (Pelclova et al., 2016c) and MWCNTs (Lee et al., 2015). Comparably, increased concentrations of 8-isoprostane in EBC (Liou et al., 2017) and enhanced fractional exhaled nitric oxide were reported in workers exposed to metal oxide ENMs (Wu et al., 2014), also when the analysis was stratified according to the type of NM exposure (SiO_2, TiO_2, indium tin oxide-NPs), while potential fibrotic and pro-inflammatory biomarkers were detected in the sputum of MWCNT-involved workers (Fatkhutdinova et al., 2016). Conversely, in research laboratory workers handling ENMs, no significant alterations in exhaled nitric oxide could be detected (Glass et al., 2017).

Alterations in blood acute-phase proteins and cytokine concentrations were also detected in animal models through acute to sub-acute administrations of different types of metallic or metal oxide-NPs such as TiO_2- (Park et al., 2009), CeO_2- (Nalabotu et al., 2011; Srinivas et al., 2011), Fe_3O_4- (Chen et al., 2010; Park et al., 2010; Srinivas et al., 2012)-, Ag- (Holland et al., 2015, 2016), and SiO_2-NPs (Downs et al., 2012; Du et al., 2013; Lu et al., 2011) as well as with carbon-based NPs (Erdely et al., 2009). Interestingly, such preclinical alterations, whatever the biological matrix employed, may function both as indicators of early effects before clinical manifestations may occur and as indirect markers of exposure although with a low specificity for ENMs (Aragon et al., 2017; Erdely et al., 2009; Shvedova et al., 2016).

3.2.2. Pathological alterations—Pathological alterations pertain to a greater understanding of the potential for adverse effects following exposure. In highly exposed nanoscale carbon black workers, alterations in pulmonary functional parameters were observed compared to controls. This suggests possible adverse respiratory alterations (Zhang et al., 2014), although other investigations failed to detect such changes in MWCNT (Lee et al., 2015; Liao et al., 2014; Vlaanderen et al., 2017) and TiO_2-NP exposed employees (Pelclova et al., 2016c, 2017b) as well as in workers handling ENMs in research laboratories (Glass et al., 2017).

Interestingly, a significant dose-dependent increase in the pulmonary surfactant protein D serum levels, as a biomarker of lung damage, was detected in workers employed in a packaging workshop of a nano-TiO_2 manufacturing plant in eastern China (Zhao et al., 2018). In these workers, alterations in cardiovascular disease markers, i.e., VCAM-1, ICAM-1, LDL, and TC, were associated with occupational ENM exposure (Zhao et al., 2018). Haematological alterations were reported in animals after oral or intra-gastric exposure to ZnO-NPs (Park et al., 2014) and TiO_2-NPs (Vasantharaja et al., 2015) as well as after dermal exposure to hydroxyapatite-NPs (Parayanthala Valappil et al., 2014), while could not be detected after a sub-acute inhalation of CeO-NPs (Gosens et al., 2016). Increased ALT concentrations and decreased albumin levels in serum as markers of

hepatocyte injury, confirmed also by histopathological alterations, were reported in rats intratracheally instilled with CeO_2-NPs (Nalabotu et al., 2011). The hepatotoxic potential of ENMs has been also documented in animals orally treated with ZnO- (Park et al., 2014), Ag-, and Au-NPs (Shrivastava et al., 2016). Significant nephrotoxic alterations principally induced by metallic NPs have been demonstrated through the assessment of the kidney injury molecule-1 (KIM-1) urinary level (Blum et al., 2015; Iavicoli et al., 2016) as well as by the BUN and creatinine serum biomarkers following an oral exposure to Cu- (Chen et al., 2006; Lei et al., 2008; Liao and Liu, 2012; Sarkar et al., 2011), Au- (Shrivastava et al., 2016), and mesopourus silica-NPs (Li et al., 2015). Indicators for the abovementioned alterations may function as potential biomarkers helpful to define target organs of ENM toxicity and, in turn, suggest potential pathological health conditions susceptible to be aggravated by ENM exposure.

3.2.3. Genotoxicity—Due to their small particle size, large surface area, and physico-chemical characteristics, NPs exhibit unpredictable genotoxic properties. Studies on workers failed to show genotoxic effects (Liao et al., 2014; Liou et al., 2012) while a general dose-dependent increase in DNA strand breaks and micronucleus (MN) frequency was found in human peripheral blood cells treated in vitro with metal or metal oxide-NPs (Colognato et al., 2008; Di Bucchianico et al., 2013; Flower et al., 2012; Ghosh et al., 2010, 2012, 2013; Kang et al., 2008, 2011; Paino et al., 2012; Soni et al., 2017; Tavares et al., 2014), carbon-based NPs (Cveticanin et al., 2010; Öner et al., 2017; Tavares et al., 2014), and dendrimers (Ziemba et al., 2012). Concerning in vivo results, a significant increase in such parameters was detected in the peripheral blood cells of TiO_2- (Song et al., 2012; Trouiller et al., 2009) and ZnO-NP treated animals (Patil et al., 2016), as compared to controls, and a dose-dependent increase in DNA fragmentation percentage was detected in lymphocytes of SiO_2 and Fe_2O_3-NP treated rats (Jiménez-Villarreal et al., 2017). However, positive results were not always confirmed and conflicting results were reported also for other metallic or metal oxide ENMs (Balasubramanyam et al., 2009; Chen et al., 2014; Cordelli et al., 2017; Downs et al., 2012; Lindberg et al., 2012; Sadiq et al., 2012; Singh et al., 2013a, b; Song et al., 2012; Tiwari et al., 2011). This may suggest a possible influencing role of different ENM physico-chemical features, routes of exposure, and administered doses.

3.3. “Omic techniques” for hazard identification

Traditional toxicology is rapidly evolving into a system-based approach, able to capture almost all the interactions between living systems and endogenous and/or exogenous xenobiotics (Balbo et al., 2017). “Omic” techniques may reveal methods helpful to assess a wide range of biological responses induced by ENM exposures, therefore, they may be promising tools for the development of novel biomarkers of exposure and early effect (Fadeel, 2015; Schulte and Hauser, 2012). These techniques currently include genomics, transcriptomics, proteomics, and more recent approaches, such as metabolomics, and adductomics involved into gene expression and its consequences.

3.3.1. Genomics—Genomic studies may provide the opportunity to detect injury at the molecular level and the signaling pathways involved in organ damage long before the clinical symptoms occur (Andersen and Krewski, 2009; Klaper et al., 2014). Several

toxicogenomic studies have investigated the in vitro and in vivo response, principally pulmonary gene expression changes, to NMs using DNA microarray analysis (Aydın et al., 2017; Costa et al., 2018; Decan et al., 2016; Ellinger-Ziegelbauer and Pauluhn, 2009; Gao et al., 2012; Husain et al., 2013; Li et al., 2013, 2017; Pacurari et al., 2011; Snyder-Talkington et al., 2015). However, accessible and more easily applicable biological matrices, i.e., blood or peripheral blood cells, have been rarely employed to assess systemic alterations; determining these correlations in animal models is an important part of practical biomarker validation. The expression of genes involved in immune, inflammatory and oxidative stress responses was affected by Au-NP-oligonucleotide complexes in human peripheral blood mononuclear cells (Kim et al., 2012), by graphene oxide also functionalized with amino groups in T lymphocytes and mononuclear cell lines (Orecchioni et al., 2017). In in vivo experiments, blood expression changes in genes involved in inflammation, oxidative stress, growth factors, tissue remodeling, and endothelial function were obtained in circulating blood cells of animals treated with SW- or MWCNTs (Erdely et al., 2009).

3.3.2. Transcriptomics—Transcriptomics aims at quantifying changes in gene expression through the enumeration of the number of mRNA copies (Costa and Fadeel, 2016). A significant increase in the mRNA expression of KL-6, a marker for the diagnosis and monitoring of interstitial lung diseases, as well as its up-stream and down-stream genes, were detected in accessible biological matrices, i.e., whole blood and sputum samples collected from workers exposed to MWCNTs compared to controls (Fatkhutdinova et al., 2016; Shvedova et al., 2016). In vitro studies also reported mRNA expression changes in macrophages exposed to mesoporous silica-NPs and PEGylated mesoporous silica-NPs at doses that do not elicit acute cytotoxicity (Yazdimamaghani et al., 2017). Numerous blood mRNAs were significantly up- or down-regulated post-MWCNT inhalation in animals developing lung pathological changes (Dymacek et al., 2015; Snyder-Talkington et al., 2013, 2016). Therefore, changes in blood mRNA expression, may potentially serve as suitable biomarkers for ENM-induced lung pathological changes, providing less invasive measurements, compared to tissue analysis, that can be taken at shorter intervals with lower costs (Snyder-Talkington et al., 2016).

3.3.3. Proteomics—Proteomic investigation may be helpful to identify candidate protein biomarkers for the evaluation of ENM early effects (Matysiak et al., 2016). In vitro results reported differently expressed proteome profiles related to cellular viability, oxidative stress, and heat response processes in human lung cells exposed to MWCNTs (Phuyal et al., 2018) as well as in the human monocytes treated with to Au-, CuO-, and CdTe-NPs (Tarasova et al., 2017). On the other hand, in vivo studies demonstrated an affected expression of proteins associated with metabolism, oxidative stress, and immune responses following TiO_2-NP inhalatory exposure (Maurer et al., 2016). More recently, the possible employment of proteomic analysis for the detection of protein carbonylation patterns as persistent, sensitive, and indirect biomarkers of ENM induced oxidative stress reaction has been explored (Driessen et al., 2015; Riebeling et al., 2016). Overall, the suitability of these proteomic changes as biological indicators of effect should be firstly confirmed by traditional biochemistry, thus supporting their effectiveness in detecting early NP toxicity.

3.3.4. Metabolomics—Metabolomics is the comprehensive analysis of all the metabolites of an organism or specified biological samples (Robertson et al., 2011). In vitro metabolomic data, demonstrated that CeO-, SiO_2- and CuO-NPs could affect the lipidome profile, and compromise the Phase II conjugational capacity in exposed hepatic cells (Kitchin et al., 2017). Differently hydroxylated or carboxylated functionalized CNTs induced alterations in amino acid metabolisms in hepatic and bronchial cells (Chatterjee et al., 2017) while an antioxidant effect was observed for chitosan-coated or ceria supported-Au-NPs in human peripheral blood cells (Palomino-Schätzlein et al., 2017). Concerning the metabolic profiling of ENM effects, as a rapid in vivo screening for nano-toxicity biomarkers, analyses performed in serum and urine of rats treated with Cu- (Lei et al., 2008) and TiO_2-NPs (Bu et al., 2010; Tang et al., 2010, 2011) provided evidence for the hepatotoxicity, nephrotoxicity and alterations in energy metabolism induced by these NPs. Other studies reported the ability of Ag- (Hadrup et al., 2012; Xie et al., 2018), Fe_2O_3-(Feng et al., 2010), SiO_2-NPs (Lu et al., 2011; Parveen et al., 2012), carbon 14-labeled C60 fullerenes (Sumner et al., 2010) and CNTs (Lin et al., 2013) to affect the liver, energy, lipid, glucose, and amino acid metabolism as assessed by the alterations found in serum and urine metabolic pathways, while amorphous SiO_2, zirconium dioxides, and barium sulphate-NPs failed to show a relevant impact on plasma metabolome patterns (Buesen et al., 2014). Although interesting, the different and not always well characterized ENMs employed, as well as the lack of standardized analytical techniques and procedures, make the results difficult to compare, and no definite conclusions to be extrapolated.

3.3.5. Adductomics—Adductomic approaches have been developed to comprehensively describe toxicological features in response to a genotoxic xenobiotic insult (Hemeryck et al., 2016; Villalta and Balbo, 2017). Specific classes of DNA adducts are those resulting from the reaction of ROS (%OH) with DNA, i.e., the 8-hydroxy-deoxy-guanosine (8-OH-dG). In field studies, 8-OH-dG concentrations were measured in easily available biological matrices collected from exposed workers, although with variable results. While no significant alterations were detected in urine, and plasma samples from employees of 14 manufacturing plants in Taiwan (Liao et al., 2014; Liou et al., 2012), increased concentrations were more recently reported in urine and white blood cells of workers exposed to metal oxide ENMs, whatever the type of ENM was considered (Liou et al., 2016, 2017), and in EBCs obtained from TiO_2-NP exposed subjects (Pelclova et al., 2016b). This DNA damage has been also investigated in vitro models exposed to metal or metal oxide ENMs, which demonstrated significant increases (Ng et al., 2017) although with a cellular type specificity (Mahmoud et al., 2016), and in Ag-NP treated animals that showed increased urinary concentrations of this biomarker (Chuang et al., 2013). The field of DNA adduct research is a highly promising area due to their potential. This is primarily related to the fact that, for instance, adducts may be interpreted as indicators of internal doses, biologically effective dose, and early effect, as well as susceptibility. Though the need exists to be validated specifically for each purpose.

3.3.6. Epigenetics—Epigenetics refers to heritable, reversible changes in gene expression occurring without alterations in DNA sequence (Shyamasundar et al., 2015; Sierra et al., 2016). DNA methylation, histone tail, and microRNA modifications are

considered useful epigenetic markers. Recent research demonstrated that CNTs (Brown et al., 2016; Chatterjee et al., 2017; Li et al., 2016; Öner et al., 2017; Tabish et al., 2017), Au-(Tabish et al., 2017), TiO_2-(Bai et al., 2015; Patil et al., 2016), SiO_2-(Gong et al., 2010, 2012; Mytych et al., 2017), ZnO-(Choudhury et al., 2017), and CuO-NPs (Lu et al., 2016) were able to induce changes of specific methylation patterns, including tumor suppressor-, inflammatory-, and DNA repair genes in vitro and in vivo models. Interestingly, a significantly lower global DNA methylation in white blood cells collected from workers exposed to nanoscale indium tin oxide in plants in Taiwan was recently reported by Liou et al. (2017), while Ghosh et al. (2017), although failing to detect significant differences in global methylation, found significant changes in genespecific DNA methylation in MWCNT exposed workers compared to controls.

Histone conformational modifications may either facilitate or depress the access of transcriptional machinery to the promoter region of some genes, leading to gene silencing or activation, respectively. As concerns ENMs, a global hypoacetylation in human breast carcinoma cells causing transcriptional repression of anti-apoptotic genes, thereby promoting cellular death, was detected after cadmium telluride quantum dots exposure (CdTe-QDs) (Choi et al., 2008). Ag-NPs were reported to affect histone post-translational modifications thus inducing a reduction in hemoglobin levels in mouse erythroleukemia cells (Qian et al., 2015). Non-coding microRNAs have been investigated in an attempt to identify fine, regulator molecules in ENM induced toxicity since they can modulate gene expression through the interaction with other epigenetic processes (Zhao et al., 2016; Peschansky and Wahlestedt, 2014). The changes in the microRNA expression profiling induced by exposure to Fe_2O_3-NPs, CdTe-QDs, Au-, Ag-NPs and MWCNTs were demonstrated to globally affect the mRNA and protein output of human treated cells, subsequently affecting many key biological patterns (Eom et al., 2014; Li et al., 2011a, b; Ng et al., 2017). Micro-RNA expression changes, implicated in inflammation and immune reactions, were found in the lungs of mice intratracheally exposed to TiO_2-NPs (Halappanavar et al., 2011). Changes in the blood levels of liver-specific miRNAs were identified in mice exposed to SiO_2-NPs (Nagano et al., 2013). However, as the functional consequences of the above mentioned epigenetic alterations were not assessed, further characterization of miRNA responsive genes and their role in adverse effects need to be defined.

4. Exposure assessment

Exposure assessments primarily involve area and breathing zone monitoring, job-exposure matrix modeling, or exposure-banding (Kauppinen et al., 2014; Moretto, 2015; NIOSH, 2009, 2017). Although, in recent years, there has been a growth of strong literature on task-based environmental monitoring (Asbach et al., 2017; Brouwer, 2010; Brouwer et al., 2012; Eastlake et al., 2016; Methner et al., 2010a,b,2012), some challenging issues, including determining the best measurement metrics, availability of appropriate instrumentation, and diverse sampling strategies, prevent an adequate assessment of environmental exposure levels. Therefore, human biomonitoring (HBM) may function as a complementary means for exposure assessment that can take into account the inter-individual variability in absorption,

metabolism, and excretion; the individual workload; and recent versus past exposure (Manno et al., 2010).

Currently there are no examples of HBM as a part of routine assessment of workers exposed to ENMs and no regulatory requirements are available for HBM. Nonetheless, there is a growing body of toxicological research that illustrates the possibility to verify some functional alterations detected in experimental settings as biomonitoring indicators for workers. For example, some ENMs can be detected in biological matrices, including blood or plasma, urine, and feces. Following metal- or metal-oxide-based ENM exposure, both via the inhalation or the intratracheal exposure (Balasubramanian et al., 2013; He et al., 2010; Semmler-Behnke et al., 2008; Sundarraj et al., 2017; Sung et al., 2009; Takenaka et al., 2001, 2006; Yu et al., 2007; Zhu et al., 2009) and via human skin application (Gulson et al., 2010, 2012), the elemental metal content is retrievable in blood, although generally in very small amounts. A positive dose-response relationship between the inhaled Ag-ENM and the Ag blood content was demonstrated in mice (Sung et al., 2009), although a differential size dependent biodistribution was reported for gold (Au)-NPs, because smaller 7-nm sized Au-NPs produced a greater metal content in blood compared to their larger 20-nm counterparts (Balasubramanian et al., 2013).

The duration of exposure can affect the interpretations of biomonitoring data, in fact, significant Ag-ENM accumulation in blood was evident after 15 days of treatment, but not following a shorter 5 day period of exposure. This suggests that the body burden of the ENMs is influenced by homeostatic processes (or the exposure could also be influencing homeostatic activities) rather than by the extent of the exposure (Iavicoli et al., 2014a,b). Detectable metal concentrations were reported also in urine samples collected from animals treated with metal or metal oxide ENMs via the respiratory or the dermal route of exposure (Balasubramanian et al., 2013; Gulson et al., 2010, 2012; Sundarraj et al., 2017; Zhu et al., 2009), but there would be no relationship described for any effect. Because of macrophage-mediated clearance mechanisms, the measurement of the elemental metal content in feces may be useful to evaluate the recent/current respiratory exposure to metal-NPs (Balasubramanian et al., 2013; Chuang et al., 2013; Li et al., 2016; Sundarraj et al., 2017e; tZahlu., 2009). However,it is rather difficult to routinely employ feces as a suitable biological matrix for occupational biomonitoring.

Exhaled breath condensate (EBC) is a promising matrix for human biological monitoring investigation, as demonstrated by the increased Ti levels in pre- and post-shift EBC samples collected from workers exposed to TiO_2-NPs in a pigment production plant compared to unexposed controls (Pelclova et al., 2015, 2016b). Interestingly the biological levels of such an indicator resulted positively correlated with the environmental concentrations in different production or research areas of the plant. However, not all ENMs are easily found in body fluids. Carbon nanotubes are one example. In fact, there is minimal transport of carbon nanotubes from the alveoli to the blood, and they tend to move out of the blood rapidly in to various organs (Erdely et al., 2009).

5. Risk assessment

Taking into account what was previously described for ENM hazard assessment and exposure evaluation, it is possible to perceive the difficulties in defining suitable risk assessment strategies. Biological monitoring data, including biomarkers of exposure and effect, can be used in risk assessment involving nanomaterial workers, but thus far, there are no examples where biomarkers have been used in risk assessments. In this scenario, an exposure-response modeling should be pursued to fully exploit the potential of possible exposure indicators. In fact, when the dose-response relationship is defined, the biomarker of exposure does not only indicate the dose actually adsorbed but provides also a reasonably accurate quantitative estimate of the occupational risks at the group and/or individual level (Iavicoli et al., 2014a). Additionally, scientific efforts should be focused at employing biological monitoring data to develop occupational exposure limits for ENM workers. To do this, the relationship between biomarker levels and adverse effects must be clearly demonstrated in a study design that includes no-effect exposure levels.

The efforts involving categorical approaches to developing occupational exposure limits (OELs) are beginning to identify biomarkers to predict toxicity. For example, the Nanosolutions project tested 31 different engineered ENMs and, out of 8 million data points, identified 11 biomarkers that support the toxicity of these xenobiotics (Nanosolutions, 2018). The response of these markers at human exposure levels must be determined. The 11 biomarkers will then be applied in untested engineered ENMs. These and other approaches that used ENMs with known hazards and the biomarkers of effect related to them may ultimately be used in dose-response modeling.

Another area that involves biomarkers that may be useful in risk assessment and OEL development for ENMs is the use of “omic” technologies that may be useful to understand the interactions and specific pathways impacted by different ENMs. Such biomarkers should be carefully verified in accessible biological matrices under low-dose, long-term conditions of exposure to define their specificity for different ENM insults, their predictive value, and therefore their realistic applicability. Investigations of the effect of functional silica ENMs on a human lung carcinoma cell line showed that it is possible to identify an “omic” analog to the NOAEL involving a no observed transcriptomic effect level or NOTEL (Pisani et al., 2015). This is the level of transcriptomic effect below which cellular responses are not seen to occur and may be much lower than the NOAEL. It could be used as a point of departure in deriving reference values. The development of pathways depicting the sequence of events between exposure to a stressor, progressing through intermediate events, and culminating in an adverse outcome is a growing concept for use in risk assessment (OECD, 2017). This concept may be increasingly used by regulatory agencies and, consequently, there may be more pressure for biomonitoring related to it.

Another relevant contribution to possible ENM-tailored risk assessment processes can be derived from epidemiologic studies. The review of the “first wave” of epidemiological studies of NM workers showed that most were too limited to indicate risk, although some found increased biomarkers of oxidative stress and inflammation in exposed workers (Liou et al., 2015). However, exposure assessment was generally qualitative, study designs were

generally cross-sectional, and various selection biases were possible. Therefore, suitable epidemiological research should be planned in order to verify environmental exposure to ENMs and their relationships with biological indicators of exposure and effect. However, no examples where biomarkers have been used in such process are currently available. Studies aimed to address the effectiveness of control technology in a nanomaterial workplace should be pursued not only as a primary way to test control effectiveness in workplaces but also as a useful mean to demonstrate the failure of prevention (Kreider and Halperin, 2011). It could be possible, in laboratory studies, to evaluate control designs and utilize a biomonitoring component of laboratory animals to supplement airborne exposure measures. Biological monitoring may be even more important, in consideration of the possible absorption of ENMs through the dermal route of exposure especially in conditions of compromised skin integrity due to pre-existing diseases or damaging coexposures (Brouwer et al., 2012; Gulson et al., 2010, 2012; Larese Filon et al., 2016; Osmond-McLeod et al., 2014).

6. Risk management

Biomonitoring is a risk management tool along with workplace exposure assessment and exposure controls. In this context, biological monitoring data could be used effectively to verify the efficacy of the exposure limit in protecting the health of the workers (Iavicoli et al., 2014a,b). At present, the utility of biomonitoring nanomaterial workers depends on the status of evidence about the hazard of particular ENMs that could be the target of biomonitoring. Biomonitoring should not be used as a substitute for controlling exposure or for taking precautionary control measures.

An additional application of biological monitoring in risk management is the medical surveillance of workers. This is the effort to assess asymptomatic workers for early indications of health problems. There are currently no mandated medical surveillance guidance for ENM workers except for ones involving baseline and period respiratory assessment (pulmonary function testing, x-ray) (NIOSH, 2013). No cellular or molecular biomonitoring is mandated. There is a sparse literature studying the effectiveness of medical surveillance for nanomaterial workers. Gulumian et al. (2016) conducted a review of structures of medical surveillance of nanomaterial workers and identified seven studies that met inclusion criteria. They concluded that there was very low quality of evidence that screening might detect adverse health effects associated with workplace exposures to ENMs. However, this study conflated epidemiological studies and medical surveillance and, as noted earlier, there has not been much time since first worker exposure and the possibility of identifying health effects in epidemiological studies in routine medical surveillance.

One further area of risk management that involves biomarkers of exposure and effect and shows great promise is to design out potential hazards in ENMs. This is known as prevention through design or “safety by design” (Geraci et al., 2015). The concept is illustrated by the identification of specific toxic endpoints that were observed after zebra fish were exposed to functionalized ENMs. This study allowed for the development of predictive models for the design of inherently safer ENMs. Similarly biomarkers found in large arrays in ENM studies may be the basis for material designs that will have reduced ENM hazards.

7. Research needs

For biological monitoring of nanomaterial workers to go forward, there is need for robust research to develop biological monitoring protocols (Iavicoli et al., 2014a,b). This should include the physico-chemical characterization of materials to which a population is exposed and well established understanding of toxico-kinetic and dynamic characteristics. This research may result in the determination of whether biological monitoring should measure direct parent compounds or possible metabolites or decomposition products. It may explain also the possible role of biomolecular corona formation in affecting ENM bio-disposition and, consequently, biomonitoring results.

There is an evident need to link biomarkers in experimental animals to biomarkers in humans. Candidate biomarkers must be validated with exposure and/or effects (Bergamaschi et al., 2015). Additionally, considering the extremely high doses frequently employed in experimental settings and the extremely low ENM retrieved fractions in biological fluids, potential biomarkers should be validated under low-doses and longer periods of treatment, through analytical techniques sensitive enough to address trace levels of biological markers. Moreover, the predictive significance of such biological monitoring alterations in terms of long-term effects, the influences exerted by ENM characteristics, modes and periods of exposure, and inter- and intra-individual variabilities should be assessed to define suitable biomarkers and accurate interpretation of their results.

Validation is a process—a sense of degree rather than an all-or-none-state (IPCS, 2001). Validation includes assessment not only of sensitivity, specificity, and predictive value, but also utility in studies of workers on a routine basis. Ultimately validation and developmental research to identify biomarkers for biomonitoring of workers will require human studies; these may be field, chamber, or epidemiologic studies. Such studies require attention to ethical legal and social issues. Of importance are issues of privacy, confidentiality, and notification of test and study results (Schulte and Smith, 2011).

8. Conclusion

There are no authoritative mandates or requirements currently available for biomonitoring of ENM workers. However, there is a growing body of research that is setting the stage for the use of bio-monitoring to supplement environment exposure assessments to achieve a suitable ENM risk assessment and management in occupational settings. Biomarkers may be particularly useful when exposure results in systemic effects. Biomonitoring requires the determination of the extent of the hazard of candidate nanomaterial and evidence that demonstrates biomarker presence in workers correlates with exposure. Biomarkers of effect may also be used to assess exposure and have similar developmental requirements as biomarkers of exposure with the additional need to account for non-specificity and homeostatic influences. If biomonitoring is to be used to assess early or potential health effects, there will be a need for prospective studies to support that use. Overall, there is a rich research base for biomonitoring. However, further work is required before biomonitoring workers can be routinely implemented.

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Occupational Safety and Health Actions									
	Hazard Identification		Exposure Assessment		Risk Assessment		Risk Management		
Biomarker Types	In vivo	In vitro	Biomonitoring		Exposure-Response Modeling	Epidemiological Studies	Control Effectiveness	Medical Surveillance	Prevention through Design
			Direct	Indirect					
Pathological									
Genotoxic									
Transcriptomic									
Proteomic									
Metabolomic									
Epigenetic									

Fig. 1.
Framework for literature search strategy.

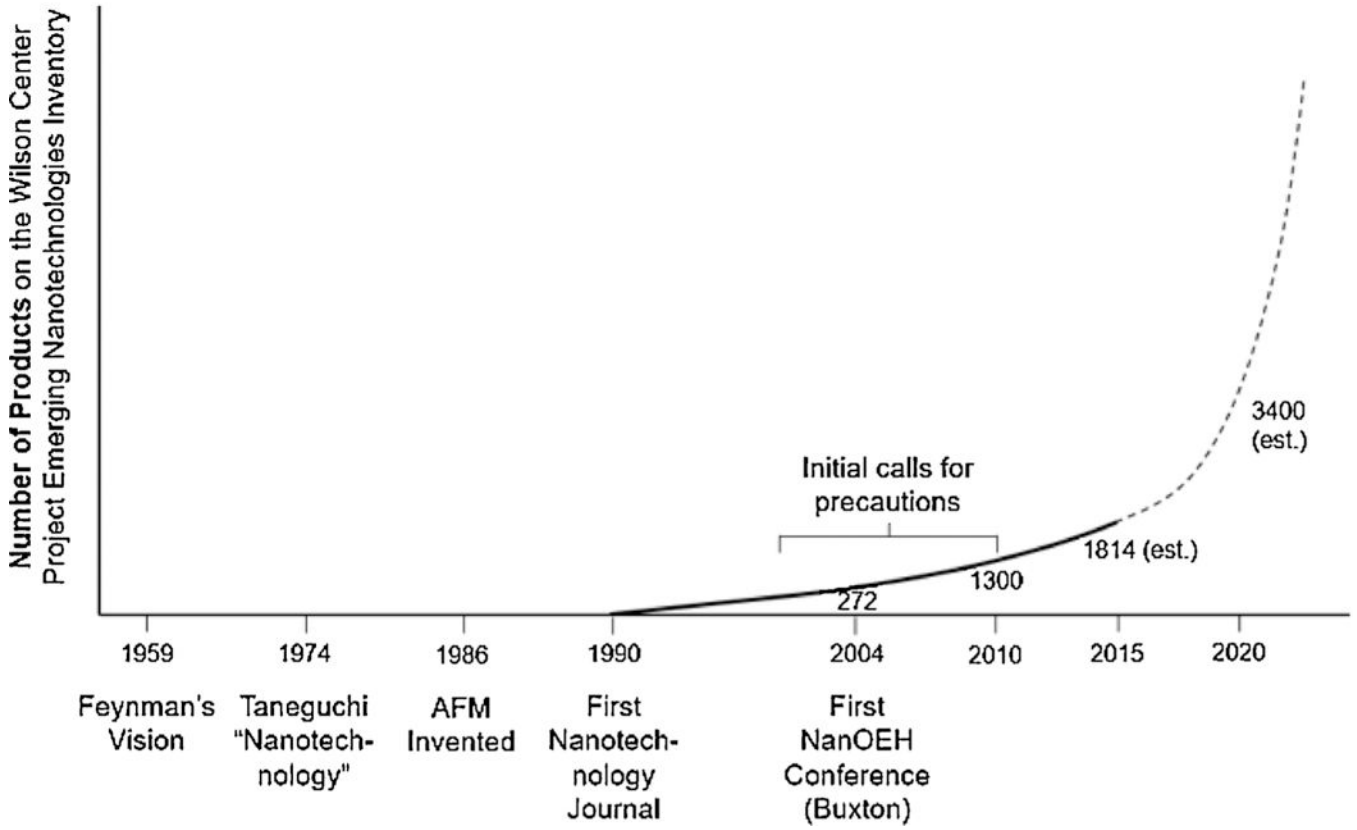

Fig. 2.
Conceptual timeline for growth of nanomaterial products.

Table 1

General Overview of Toxicology Findings for ENMs to date.

•Verified the correlation of particle surface area with biological effects (Duffin et al., 2001; Schmid and Stoeger, 2016)
•Confirmed that particle size is generally an important factor in toxicity but other physico-chemical factors may play major roles (Driscoll, 1996; Oberdörster et al., 2005)
•Confirmed that nanoparticles could reach the alveoli and could enter the interstitium and blood stream (Kreyling et al., 2009; Oberdörster et al., 1992)
•Demonstrated that pulmonary exposure to carbon nanotubes (CNTs) causes alveolar interstitial fibrosis, which develops rapidly and is persistent. Fibrotic potency appears related to the physicochemical properties of the CNT (Shvedova et al., 2005)
•Demonstrated that pulmonary exposure to nanoparticles can cause cardiovascular effects (alteration of heart rate and blood pressure, and microvascular dysfunction) (Li et al., 2007; Nurkiewicz et al., 2008)
•Demonstrated that pulmonary exposure to some nanomaterials may be carcinogenic (Kuempel et al., 2017; Rittinghausen et al., 2014; Sargent et al., 2014)
•Demonstrated that multi-walled carbon nanotubes (MWCNTs) (Mitsui-7) are a promoter of lung cancer (Kuempel et al., 2017)
•Demonstrated that nanoparticles deposited in the lung can translocate to distal sites (Aragon et al., 2017; Erdely et al., 2009; Mercer et al., 2013) Demonstrated that insoluble nanoparticles do not appear to rapidly cross intact skin (Prow et al., 2011)
•Demonstrated that nanoparticle penetration through intact skin is not likely but exposure to sensitizers and irritants still a concern (Gwinn and Vallyathan, 2006; Prow et al., 2011)